REMARKS/ARGUMENTS

Claims 31-33, 35-40, 42, 44-46 and 48 (2 independent claims; 14 total claims) remain pending in this application. No amendments have been made to the claims in this response. Reconsideration is respectfully requested in light of the following remarks.

Applicants acknowledge the Examiner's withdrawal of the previous rejection of claims 31-33, 35, 36-40 and 42 as being unpatentable over Papac et al. (Analytical Chemistry) in view of Gaskell et al. (Immunoadsorption to improve Gas chromatography/High-Resolution Mass spectrometry of estradiol-17B in Plasma). The Examiner has stated that he has withdrawn this previously issued rejection in view of Applicants' arguments presented during the telephone interview conducted December 22, 2005.

Claims 31-33, 35-40, 42, 44-46 and 48 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner states that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. More particularly, the Examiner states that the specification on page 5, lines 21-35 discloses that "the specificity of the antibody-antigen reaction coupled with the ability of the mass spectrometer to separate and unequivocally identify the captured and isolated antibody or antigen by its mass-to-charge ratio from other molecules that may accompany it lends two dimensions of specificity to the present invention." The Examiner then states that the specification does not specifically disclose a single dimension mass spectrometric analysis to resolve distinct signals and that there is no description in the specification disclosing that only single dimension mass spectrometric analysis is used to resolve distinct signals. Applicants respectfully traverse this rejection.

Applicants' specification clearly states that "the present invention combines and exploits the specificity of antibody-antigen binding and the ability of the mass spectrometer to unequivocally identify molecules in various qualitative and quantitative strategies to analyze one or more antigens or antibodies in a specimen within the limit of detection." (See page 5, paragraph 4 of Applicants' specification). Moreover, the language of Applicants' specification which the Examiner cites on page 5 specifically states that the mass spectrometer is used "to separate and unequivocally identify the captured and isolated antibody or antigen by its mass-to-charge ratio from other molecules that may accompany it," thereby lending two dimensions of

specificity to the present invention. In addition, Applicants' specification goes on to state that the mass spectrometric immunoassay of the present invention is an improvement over existing immunoassays because the detection using mass spectrometry lends an added dimension of unequivocal specificity. (See column 6, first paragraph of the Applicants' specification). Further, Applicants' specification specifically states that one improvement of the present invention over the existing immunoassays is that the presence of other substances which are not the subject of immunoassay do not interfere with either detecting or quantifying the targeted antigen or antibody. (See page 6, first paragraph of Applicants' specification). In addition, Applicants' specification specifically states the following: "Mass spectrometric analysis of the captured, isolated and unbound analyte results in an analyte mass spectral signal at the mass-to-charge ratio characteristic of the analyte. The location of the signal on the mass spectrum is dependent on the molecular weight of the analyte, thereby providing a reliable means for identifying the analyte. The mass spectral signal also has magnitude. The magnitude of the signal is indicative of the amount of analyte that is ionized and detected by the mass spectrometer. Mass spectrometric signal magnitude has at least two dimensions that are directly measurable, intensity or height of the signal, and integral or the area under the signal. Either the intensity or the integral can be used to quantify." (See page 24, second full paragraph of Applicants' specification).

Reference to mass spectrometric analysis for identifying and quantifying an analyte equivocates to single dimension mass spectrometry in that only a single mass spectrometer is used. In contrast, "tandem mass spectrometry" as known in the relevant field of art refers to two mass spectrometers connected in series by a chamber that can break a molecule into pieces. Applicants have included several references (attached hereto as Exhibit A) which discuss and define tandem mass spectrometry as involving two separate spectrometers or analyzers. Accordingly, in that Applicants only discuss the use of a single mass spectrometer in carrying out the invention, and in that Applicants only rely on and utilize a single mass spectrometer in all of the examples included in the specification, it is inherently known to those skilled in the art that Applicants' invention utilizes a single dimension mass spectrometry.

Claims 31-33, 35-40, 42, 44-46 and 48 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner states that "single dimension mass spectrometry" as used in line 12 of claim 31 is vague and indefinite. In

particular, the Examiner states that there is no definition provided for this term in the specification and that it is therefore unclear what Applicants intend. In response to the Examiner's rejection, Applicants refer the Examiner to Applicants' response to the Examiner's rejection of the claims as failing to comply with the written description requirement set out above and herein incorporates those arguments by reference in their entirety.

Claims 31-33, 35 and 36 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Papac et al. (Analytical Chemistry) in view of Gaskell (Quantification of Steroid Conjugates Using Fast Atom Bombardment Mass Spectrometry, Steroids, 1990, Vol. 55, pages 458-462). In particular, the Examiner states that Papac discloses a method for the mass spectral identification and detection of analytes separated by immunoaffinity chromatography, using antibody immobilized agarose beads as affinity columns, combining a specimen with the beads to capture antigen present in the sample (post-combination affinity reagent), washing to remove any unbound antigen, mixing sample with the beads and centrifuging and removing supernatant, adding a matrix containing formic acid to the supernatant and testing by MALDI-TOF mass spectrometry (single dimension mass spectrometric analysis), and determining the analyte by mass-to-charge ratio. Although the Examiner concedes that Papac fails to teach that the specimen is combined with an internal reference species of known concentration prior to capturing and isolating the analyte and IRS, and also failing to teach quantifying the analyte, the Examiner contends that Gaskell discloses quantifying an analyte where a deuterated internal standard is added to the sample which is then mixed with the solid phase incorporating bound antiserum for isolating the analyte and internal standard. The Examiner further contends that Gaskell discloses that for quantification of the analyte, the analyte and the internal standard are compared to a standard curve and that the standard curve was obtained by analysis of standard mixtures of the analyte and analyte analog. The Examiner also asserts that Gaskell discloses that the addition of an internal standard provides for precise and accurate data and provides for the quantification of an analyte. Accordingly, the Examiner contends that it would have been obvious to one of ordinary skill in the art to incorporate an internal standard and affinity reagent and also to develop a standard curve for quantification analysis into the method of Papac because Gaskell teaches that the addition of an internal standard provides for precise and accurate data and provides for the quantification of an analyte of interest. The Examiner further contends that one of ordinary skill in the art would have had a reasonable expectation of success by incorporating an internal standard and affinity reagent as taught by Gaskell into the method of

Papac. Applicants respectfully traverse this rejection.

First, the capturing and isolating of at least one or more analyte is performed completely differently than the process described in Papac. In particular, Papac fails to disclose releasing an isolated analyte species by alerting the analyte species from an antibody and then detecting the presence of the isolated and released analyte species using a mass spectrometer to determine whether the analyte species was present in the physiological specimen. Instead, aliquots of beads containing the predetermined analyte were removed from the column for performing MALDI/TOF analysis (see page 2611, column 1, first paragraph). The discussion under mass spectrometry on page 2611, first paragraph of the Papac reference merely describes how the sample aliquots of beads containing the known analytes were prepared for performing mass spectrometry. Further, this is clearly confirmed in the results and discussion section which states: "Purification was necessary before binding the antibody to the affinity support. To accomplish this purification, cytochrome c was first bound to the affinity support (see experimental section). The crude antibody solution was passed through the column, and a one-micro liter aliquot of the column bed was used to acquire the MALDI/TOF spectrum shown in Fig. 1A." (Papac, page 2611, bottom of column 1, top of column 2). In contrast, in Applicants' invention, the analyte species is released by eluting it from the antibody and a released analyte species is detected using a mass spectrometer to determine whether the analyte species is present in the physiological specimen, determining the identity of the analyte species using molecular weight analysis, and determining the quantity of the analyte species.

Moreover, the Gaskell reference cited by the Examiner discloses fast atom bombardment/mass spectrometry or liquid secondary ion mass spectrometry to analyze steroid conjugates (sulfates, gulcuronides) without prior hydrolysis or derivitization. In particular, the Gaskell reference describes the quantitative determination of dehydroepiandrosterone sulfate in serum by selective isolation of the analyte using immunoadsorption extraction and highly specific detection using tandem mass spectrometry. The quantification method includes 1) stable isotope dilution using an internal standard, 2) isolation of the analyte by immunoadorption, and 3) detection of both the analyte and internal standard during limited mass range parent ion scanning during tandem mass spectrometry (see page 460, column 1, fourth paragraph of the Gaskell reference). Furthermore, the Gaskell reference specifically states that "the success of the detection procedure was dependent both on the selectivity of tandem MS detection and on the achievement of a sufficiently "clean" biologic extract by immunoadsorption." (See page 461,

column 2, second paragraph of Gaskell). Accordingly, the Gaskell reference cited by the Examiner actually teaches away from the instantly claimed invention by using tandem MS for quantification. In other words, different mass spectrometric measurements were taken of similar portions of the same serum extract and compared. In contrast, in Applicants' instantly claimed invention, the analyte and IRS are measured using MS in a single measurement. Accordingly, it would not have been obvious to one of ordinary skill in the art to incorporate the method disclosed in Gaskell into the method of Papac to arrive at Applicants' claimed invention because Applicants' claimed invention would then require tandem MS. In contrast, Applicants' claimed invention requires single dimension MS.

Claims 37-40 and 42 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Papac et al. in view of Gaskell as applied to claims 31-33, 35 and 36 above, and further in view of Chiabrando et al. (Journal of Chromatography). In particular, although the Examiner concedes that Papac and Gaskell fail to teach combining a plurality of distinctive internal reference species to a sample, the Examiner contends that Chiabrando discloses adding multiple deuterated internal standards to a sample and also using immobilized antibodies to capture and isolate the analytes and internal standards. The Examiner further contends that Chiabrando discloses that this provides for the simultaneous measurement of analytes and their metabolites. Accordingly, the Examiner contends that it would have been obvious to one of ordinary skill in the art to incorporate multiple internal standards at taught by Chiabrando into the modified method of Papac because Chiabrando discloses that this provides for the simultaneous measurement of analytes and their metabolites and further because it would have been obvious to one of ordinary skill in the art to use different types of standards with the different analytes to be detected. Applicants' respectfully traverse this rejection.

Papac fails to disclose the use of combining an internal reference species with a specimen, capturing and isolating an analyte and the internal reference species contained in the specimen, and quantifying the analyte using single dimension mass spectrometric analysis to resolve signals for the analyte and the internal reference species to determine the amount of the captured analyte. Further, as previously set out above, the Gaskell reference fails to disclose using single dimension mass spectrometry and instead requires using tandem mass spectrometry for detecting an analyte and internal standard and for quantifying the analyte. Therefore, it could not have been obvious to one of ordinary skill in the art to combine Gaskell and Papac to arrive at Applicants' claimed invention which utilizes single dimension mass spectrometry to resolve

distinct signals for the analyte and the IRS to determine the amount of captured analyte. Chiabrando discloses a method which utilizes gas chromatography-mass spectrometry. Chiabrando fails to disclose the use of single dimension mass spectrometry to analyze and quantify an analyte. Therefore, it would not have been obvious to one of ordinary skill in the art to combine Chiabrando with Papac and Gaskell to arrive at Applicants' claimed invention.

Claims 44-46 and 48 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Papac et al. and Gaskell in view of Chiabrando as applied to claims 31-33, 35-40 and 42 above, and further in view of Merren. Although the Examiner concedes that Gaskell and Chiabrando fail to specifically teach interpolating the analyte species mass spectrometric response to the IRS's mass spectrometric response, the Examiner contends that Merren teaches the addition of a reference substance which provides a spectrum containing peaks at several known mass-to-charge ratios. The Examiner further contends that Merren teaches that the reference spectrum is accurately correlated with the spectrum of the unknown substance and that the reference peaks therefore act as accurate markers forming a calibrated scale from which the mass-to-charge ratios of peaks of the unknown substance are interpolated. The Examiner further states that Merren teaches that this provides a method for combining signals representative of the simultaneous spectral analysis of two substances, thereby permitting single channel processing of the combined signal. Accordingly, the Examiner contends that it would have been obvious to one of ordinary skill in the art to interpolate the analyte species in the reference species as taught by Merren into the modified method of Papac because Merren shows that this provides a method for combining signals representative of the simultaneous spectral analysis of two substances thereby permitting signal channel processing of the combined signal. Applicants respectfully traverse this rejection.

As previously stated above, it would not have been obvious to one of ordinary skill in the art to combine Papac, Gaskell, and Chiabrando to arrive at claims 31-33, 35-40 and 42 and those arguments are herein incorporated by reference in their entirety.

Furthermore, Merren discloses a double beam mass spectrometer for simultaneously enabling mass spectral analysis for two substances such as an unknown and a reference substance. Merren fails to disclose single dimension mass spectrometric analysis of an analyte and an internal reference species using a standard single beam mass spectrometer. Therefore, it would still not have been obvious to one of ordinary skill in the art to combine Merren with

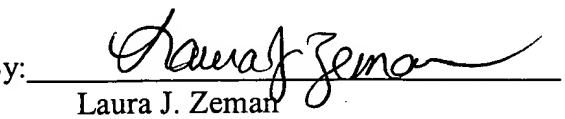
Papac and Gaskell to arrive at Applicants' claimed invention. Accordingly, it would not have been obvious to one of ordinary skill in the art to combine Merren with Papac, Gaskell, and Chiabrando to arrive at Applicants' claims 44-46 and 48.

With respect to the Examiner's response to Applicants' arguments and the Examiner's statement that the Examiner has not relied upon Gaskell for teaching tandem MS but has instead relied upon Gaskell for teaching that it is known in the art to incorporate internal references into a sample for the quantification of an analyte, Applicants reassert their argument that it would not have been obvious to one of ordinary skill in the art to combine Gaskell with Papac because Gaskell is directed to using an internal reference standard with tandem MS. Accordingly, the combination of Papac and Gaskell cannot teach a single dimension mass spectrometric process for quantifying an analyte using internal reference species.

In view of the foregoing, Applicants respectfully submit that all of the pending claims fully comply with 35 U.S.C. §112 and are allowable over the prior art of record. Reconsideration of this application and allowance of all pending claims is earnestly solicited. Should the Examiner wish to discuss any of the above in greater detail or deem that further amendments should be made to improve the form of the claims, then the Examiner is invited to telephone the undersigned at the Examiner's convenience.

Moreover, in that the instant application has been pending for several years with multiple office actions rejecting Applicants' claims, Applicants request that the Examiner allow this application to move forward to the Board of Patent Appeals and Interferences in the event that the Examiner once again fails to find allowable subject matter. In other words, Applicants respectfully request that the Examiner issue a non-withdrawable, final rejection in the event that he fails to find allowable subject matter so that this application can move on in the appeal process.

Respectfully submitted,

By: 

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